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(54) Title: BIOCOMPATIBLE METALLIC STENTS WITH HYDROXY METHACRYLATE COATING

(54) Titre: STENT METALLIQUE BIOCOMPATIBLE A REVETEMENT D'HYDROXYMETHACRYLATE

(57) Abstract

The invention provides a hemo-compatible, restenosis-inhibiting metallic stent, comprising a coating of a poly-hydroxy methacrylate derivate selected from the group consisting of poly-hydroxyethylmethacrylate (PHEMA), poly (hydroxyethoxyethyl methacrylate) (PHEEMA), poly (methoxyethyl methacrylate) (PHEEMA), poly (methoxyethyl methacrylate) (PMEMA), poly (methoxyethyl methacrylate) (PMDEEMA), poly (ethylene glycol dimethacrylate) (PEGDMA), and mixtures thereof.

(57) Abrégé

L'invention concerne un stent métallique hémocompatible, inhibant la resténose, comprenant un revêtement de polyhydroxyméthacrylate sélectionné dans le groupe comprenant le polyhydroxyéthyl méthacrylate (PHEMA), le poly(hydroxyéthoxyéthyl méthycrylate) (PHEEMA), le poly(hydroxydiéthoxyéthyl méthacrylate) (PHDEEMA), le poly(méthoxyéthyl méthacrylate) (PMEEMA), le poly(méthoxyéthyl méthacrylate) (PMEEMA), le poly(méthoxyéthyl méthacrylate) (PMDEEMA), le poly(éthylèneglycol diméthacrylate) (PEGDMA), ainsi que des mélanges de ces composés.

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54) Title: BIOCOMPATIBLE METALLIC STENTS WI	тн нү	DROXY METHACRYLATE COATING
57) Abstract		
nethacrylate derivate selected from the group consisting the property of the p	ing of	nhibiting metallic stent, comprising a coating of a poly-hydro poly-hydroxyethylmethacrylate (PHEMA), poly (hydroxyethoxyeth rylate) (PHDEEMA), poly (methoxyethyl methacrylate) (PMEM/ oxydiethoxyethyl methacrylate) (PMDEEMA), poly (ethylene glyc
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Description

BIOCOMPATIBLE METALLIC STENTS WITH HYDROXY METHACRYLATE COATING

Technical Field

The present invention relates to the application of a coating of a poly-hydroxymethacrylate derivative to improve the biocompatibility of metal stents intended for implantation or insertion. More specifically, the present invention relates to the coating of metallic stents with effective amounts of a coating of a poly-hydroxymethacrylate derivative which will drastically increase the thromboresistance of the stent, as well as prevent any significant deposit of protein, or the occurrence of mineral encrustation, and thereby achieve inhibition of restenosis.

Background Art

Advances in medical and surgical technology involving the introduction of implantation of foreign materials, such as stents, catheters, prostheses, etc. into body-tissue make the search for the development of materials that exhibit a long-term biocompatibility more pressing than ever before. A wide range of materials and polymers have been tested and used in medical device applications. These include polyethylene, polypropylene, polyvinylchloride, polyesters, polystyrene, polyurethane, silicone, polysulphone, polyamide, polytetrafluoroethylene, cellulose and its derivatives. Although they have excellent mechanical and physical properties, they were originally developed for the use in industrial manufacturing and not specifically for the biomedical field.

Foremost among the difficulties that need to be addressed within a medical or surgical context are the problems concerning the development of thromboresistant materials and coatings that will resist protein deposits and adverse vessel-wall reactions. Indeed, it is by now well-documented that adverse reactions between foreign or prosthetic surface and blood components, e.g. platelet-activation and thrombogenesis, constitute the single most important factor limiting the use of certain biomaterials. To prevent uncontrolled hemostasis, patients need to be

treated prophylactically with anti-coagulants, such as heparin or warfarin. In a considerable fraction of these cases, depending on the site of deployment of the implant, the patient needs to continue this medication indefinitely, necessitating a strictly controlled regime of drug-taking which effectively balances the patient on a narrow operational strip flanked by the dual dangers of uncontrolled bleeding on the one hand and the development of an embolism on the other, both obviously equally disastrous outcomes. Even if this treatment can be discontinued after a limited period of time, it complicates the procedure and significantly increases the

As a matter of fact, some biomedical applications are totally precluded by the thrombogenic potential of stents and/or synthetic polymers. An example of this is the small diameter vascular graft for use in coronary artery bypass. At present, all synthetic materials fail in this application and a patient requiring coronary bypass must first undergo a procedure to remove the saphenous vein from the leg. This vein is subsequently used to carry out the bypass itself. A biocompatible material would have an enormous benefit in this application.

patient's risk of post-operative bleeding and infection.

With regard to the problem of protein deposition, this manifests itself whenever biological fluids come into contact with synthetic surfaces such as glass, steel or polymers. These deposits have an important impact on the course of subsequent events occurring at the surface such as platelet adhesion-activation for blood containing devices, or mineral encrustation on urological stents. The risk of thrombus formation is, in the case of some devices, also accompanied by the additional risk of infection as a result of the adhesion and proliferation of bacteria at the surface of a biomaterial.

Numerous experiments have been conducted aiming at improving the biocompatibility of stents and surgical implant-devices. Based on the experimental data, one of the most recent suggestions is to use an amphiphilic polyurethane coating on stents (see e.g., De Scheerder et al.: Biocompatibility of biodegradable and non-biodegradable polymer coated stents in porcine peripheral arteries. Cardiovasc. Intervent. Radiol. 18:4, Jul-Aug. 1995, pp.227-32).

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Another approach is based on a discovery made by Chapman in the late 1970's I See e.g., Chapman, D., et al.: Biomembranes as models for polymer surfaces. Biomaterials. Vol. 7, July 1986, pp. 121-5, 126-31 and 252-8; Durrani, AA, Hayward, JA and Chapman, D: Biomembranes as models for polymer surfaces II; The syntheses of reactive species for covalent coupling of phophorylcholine to 1986 Biomaterials, 7:2. surfaces. pp. 121-5; Hall, B., et al.: Biomembranes as models for polymer surfaces. Biomaterials. Vol. 10, May 1989, p.219-224; and Hayward, JA, et al.: Biomembranes as models for polymer surfaces IV; ESCA analyses of a phosphorylcholine surface covalently bound to hydroxylated substrates. Biomaterial, 7:4, 1986 Jul. pp. 252-8], who observed that intact biological membranes are highly successful in preventing inappropriate blood clotting reactions. He went on to show that the phosphorylcholine head group is essential in imparting biocompatability to the phospholipids in the cell-membrane. Some of the most promising and successful attempts of designing biocompatible coatings to properties: by covalently binding a try to harness these phosphorylcholine-group to a metal or polymer they attempt to mimic the external surface of biomembranes.

Disclosure of the Invention

The present invention is based on a different approach. Instead of coating the stent with polyurethane or any of the other polymers cited above, according to the present invention, a coating of a poly-hydroxy methacrylate derivative is applied to a metallic stent which results in a highly biocompatible and thromboresistant coating for said stents.

More particularly, according to the present invention there is now provided a hemo-compatible, restenosis-inhibiting metallic stent, comprising a coating of a poly-hydroxy methacrylate derivative.

The term poly-hydroxy methacrylate derivative, as used herein, is intended to nclude hydroxy, alkoxy, and dihydroxy, i.e. glycol derivatives.

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More specifically, the present invention provides a hemo-compatible, restenosis-inhibiting metallic stent, comprising a coating of a poly-hydroxy methacrylate derivative selected from the group consisting of poly-hydroxyethylmethacrylate (PHEMA), poly (hydroxyethoxyethyl methacrylate) (PHEEMA), poly (hydroxydiethoxyethyl methacrylate) (PHDEEMA), poly (methoxyethyl methacrylate) (PMEMA), poly (methoxyethyl methacrylate) (PMEEMA, poly (methoxydiethoxyethyl methacrylate) (PMDEEMA), poly (ethylene glycol dimethacrylate) (PEGDMA), and mixtures thereof.

In another aspect of the present invention there is now provided a process for producing hemo-compatible, restenosis inhibiting metallic stents including the steps of:

- (a) coating a metallic stent with a liquid which contains a hydroxymethacrylate derivative selected from the group consisting of 2-hydroxyethyl-methacrylate; hydroxyethoxyethyl methacrylate, hydroxydiethoxyethyl methacrylate, methoxyethyl methacrylate, methoxyethoxyethyl methacrylate, ethylene glycol dimethacrylate and mixtures thereof;
- (b) polymerization of said 2-hydroxy-methacrylate derivative into a polyhydroxymethacrylate derivative selected from the group consisting of poly-hydroxyethylmethacrylate (PHEMA), poly (hydroxyethoxyethyl methacrylate) (PHEEMA), poly (hydroxydiethoxyethyl methacrylate) (PHDEEMA), poly (methoxyethyl methacrylate) (PMEMA), poly (methoxyethyl methacrylate) PMEEMA, poly (methoxydiethoxyethyl methacrylate) (PMDEEMA), poly (ethylene glycol dimethacrylate) (PEGDMA), and mixtures thereof;
- (c) cleaning the stent after polymerization to extract any remaining residues; and
 - (d) drying the same.

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The present invention also provides a process for producing hemo-compatible bioactive restenosis inhibiting metallic stents, comprising the steps of:

a) coating a metallic stent with a liquid which contains poly-hydroxyethylmethacrylate in liquid form;

- b) cleaning the stent to extract any remaining residues; and
- c) drying the same.

Summary of the invention

Unlike the approach pioneered by Chapman (Ibid), the present invention does not aim at mimicking the cell-membrane directly. Rather, the aimed-for biocompatibility is achieved by applying a coating of a poly-hydroxymethacrylate to the metallic surface of a stent. Current uses of 2-hydroxyethyl-methacrylate (hereinafter referred to as HEMA) or its polymer (hereinafter referred to as PHEMA) include adhesives, artificial nails, lacquers, cosmetic compositions, UV-inks and soft lens applications. Surfaces of plastic devices are modified with PHEMA. Furthermore, it is also used as an anti-adhesive to prevent cell attachment in cell cultures, and as an inducer of trabecular bone in dental implants. As such, its non-toxicity and usefulness in medical and biological applications is well-documented.

According to the present invention poly-HEMA is used as a biocompatigenic coating for metal stents. This PHEMA coating renders the stents biocompatible by covering the metallic surface with a uniformly distributed layer of strongly polar and hence hydrophilic groups. As stated hereinbefore, in addition to PHEMA, there are other acrylic-type polymers which are poly-hydroxymethacrylate derivatives and which are similar in general structure to PHEMA:

Among these derivatives are poly (hydroxyethoxyethyl methacrylate) (PHEEMA), poly (hydroxydiethoxyethyl methacrylate) (PHDEEMA), poly (methoxyethyl methacrylate) (PMEMA), poly (methoxyethyl methacrylate) PMEEMA, poly (methoxydiethoxyethyl methacrylate) (PMDEEMA), and poly

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(ethylene glycol dimethacrylate) (PEGDMA). The use of all these polymers and combinations thereof as coating on metallic stents is part of the present invention, although the invention will now be more specifically described with reference to the preferred PHEMA coating, it being understood that the description with regard to PHEMA is also applicable to said other polymeric coatings.

In a first preferred embodiment of the present invention the polymerization of the HEMA takes place directly on the metallic surface of the stent.

In a second preferred embodiment of the present invention the HEMA is polymerized partly before it comes to the surface of the stent.

In U.S. Patent 5,679,400 there is described a method for providing a therapeutic substance into a body lumen which involves providing a stent and applying to the stent a solution which includes a solvent, a polymer dissolved in the solvent and a therapeutic substance dispersed in the solvent. The polymers described in said patent include bioabsorbable polymers such as poly(lactic poly(lactide-co-glycolide) and poly(hydroxbutyrate-co-valerate) and biostable polymers such as polyurethanes, silicones, polyesters, vinyl homopolymers and copolymers, acrylate homopolymers and copolymers, polyethers and cellulosics, however said patent does not teach or suggest the specific use of a coating of a polyhydroxymethacrylate derivative to a stent in the substantial absence of a therapeutic component in order to provide restenosis-inhibiting properties to said stent and the only acrylate polymer mentioned in said patent is an ethylene-methyl methacrylate copolymer, listed as one among tens of other named polymers.

Several explanations may be offered for the biocompatigenic nature of PHEMA. One possibility is that the strongly hydrophilic nature of the outside layer of PHEMA attracts a dense water-coat, thus preventing blood-corpuscies to come into direct contact with the stent, an event that normally triggers the thrombogenic reaction (see, e.g., Binderman, I., et al., Grafts of HTR Polymer versus Kiel Bone in Experimental Long Bone Defects in Rats, ASTM, PA 19103).

Alternatively, it may be the case that polar PHEMA coating attracts the polar moiety on circulating phospholipids which then precipitate under the form of a lipid bilayer. In this instance, biocompatibility would again be a consequence of mimicking the thromboresistance of cell-membranes. If this latter hypothesis turns out to be correct, it underscores the possibility of self-assembly and hence self-repair of the very factor that induces biocompatibility. This is an extremely desirable property for a stent, especially in locations where there are considerable shear forces due to strong blood-circulation, such as heart and main arteries. In addition, PHEMA coated stents prevent adverse cell reaction of the injured site, cell growth, and restenosis.

Whatever the explanation, it has now been found that coating of the metallic surface of stents with PHEMA results in the creation of a stable and highly biocompatible coating which makes the stent thromboresistant and prevents the deposition of protein and adverse vessel-wall reactions, thus vastly increasing their value in surgical procedures.

Thus, the present invention enables the prevention or minimization of restenosis that is evident in some cases with the introduction of metallic stents, by providing hemo-compatible bioactive restenosis-inhibiting metallic stents.

2-Hydroxyethyl methacrylate (HEMA) can be polymerized into poly-HEMA (PHEMA), which is a polymer exhibiting a strongly polar character. PHEMA shows minimal bacterial or cell binding but excellent cell biocompatibility, no protein deposition and no blood clotting. This means that blood plaques which might trigger the development of a potentially fatal thrombus will not be formed. As there is little or no bacterial adhesion, the risk of infections is minimized. PHEMA is a coating which can be used on metal based stents, and which makes these stents biocompatible. The stents can be made of stainless steel, Ti-based alloys, shape memory alloys or any other metal, eventually in combination with synthetic or biological materials. The stents are coated with the hydrophilic HEMA-monomer, which is then polymerized by using dielectric heating, UV light, electron-beam

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radiation, gamma-radiation, ozone initiation, X-rays, lasers, visible light, thermal cure or any other means. Thus, said polymerization can be initiated by at least one of photopolymerization, ionic-polymerization, and chemical-polymerization.

After the polymerization procedure, the stent is placed in hot or boiling liquid, e.g. water to remove the remaining monomers. Such stents find applications in e.g. vascular, endo-esophageal and urological stents, as well as for coronary artery bypass surgery or the repair of aneurysms, etc. .

In general, the procedure for preparing coated stents according to the present invention is as follows:

A stock solution is prepared by dissolving the 2-hydroxyethyl methacrylate (HEMA), formula $C_{\rm g}H_{10}O_{\rm 3}$, CAS Number 868-77-9, in ethanol. Other possible solvents are dimethyl sulfoxide (DMSO), propanol, glycerol, ethylene glycol, cyclohexanol, toluene and dimethyl formamide (DMF). It is preferable to use the HEMA in an as pure as possible form, typically better than 98.4%. Typical solutions are made by dissolving 120 mg HEMA in 1 ml 95% ethanol. The dissolving process is helped by shaking the solution and a storage at e.g. 37°C for 12 hrs. A separation of undissolved material can be reached by centrifuging at e.g. 2500 rpm for 30 min. Further dilution with ethanol can be used to produce coatings of various thickness. Polymerization is lightly inhibited by trace amounts of an inhibitor such as the methyl ether of hydroquinone (MEHQ). MEHQ should be present in a concentration within the range of 150 to 300 ppm, preferably 200 ppm. The HEMA can be modified by the addition of a cross linking agent such as triethyleneglycol dimethacrylate, which comprises between about 0.1 and 6% of the Alternatively, tetraethylenglycol dimethacrylate, HEMA, preferably 5%. diethyleneglycol dimethacrylate and monoethyleneglycol dimethacrylate can be used. A combination of these diesters can also be used.

After wetting the stents with the described solution, they can be air dried in a e.g. sterile environment (sterile lamina flow hood), or when inhibitors are applied, the polymerization can take place by means of a dielectric furnace, UV light or

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controlled temperature chamber. The heating provides sufficient free radical activity to overcome the effect of the inhibitor, resulting in polymerization of the coating. The heating step is, e.g. about 1.5 minutes in duration in a dielectric furnace when the upper electrode is positioned about 5 mm above the stent. In order to remove any remaining HEMA monomer and/or traces of the inhibitor after the polymerization step, the stent is boiled in water for about 2 to 3 minutes after cooling down. This procedure will leach out any remaining HEMA monomer and/or inhibitor. After boiling, the stents can be dried at a slightly higher temperature.

In order to further improve the biocompatibility, the surface modification by selective alkaline hydrolysis was studied. It was found that the thickness of the modified layer can be influenced by the reaction temperature, NaOH concentrations and reaction time.

2-hydroxyethyl methacrylate can be applied directly to the stent or with the help of

Using at least 30% NaOH, short reaction times and temperatures of at least 90° C, coatings with carboxylic groups in the surface layer were prepared. This method can be used for obtaining hydrophilic medical coatings with further improved properties and further increased biocompatibility.

The scope of the invention includes the coating with a poly-hydroxymethacrylate derivative of all metallic surfaces of stents of all types, as well for only metallic stents and for the coating of stents formed from the combination of metal with synthetic or biologic tissues.

Description of Preferred Embodiments

a primer such as silanes.

While the invention will now be described in connection with certain preferred embodiments in the following examples so that aspects thereof may be more fully understood and appreciated, it is not intended to limit the invention to these particular embodiments. On the contrary, it is intended to cover all alternatives, modifications and equivalents as may be included within the scope of the invention as defined by the appended claims. Thus, the following examples which include preferred embodiments will serve to illustrate the practice of this invention, it being understood that the

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particulars shown are by way of example and for purposes of illustrative discussion of preferred embodiments of the present invention only and are presented in the cause of providing what is believed to be the most useful and readily understood description of formulation procedures as well as of the principles and conceptual aspects of the invention.

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Example 1

10. hood).

1. A stock solution is prepared by dissolving 120 mg 2-hydroxyethyl methacrylate (HEMA), formula $C_0H_{10}O_3$, CAS Number 868-77-9, in 1 ml 95% ethanol. It is preferable to use the HEMA in an as pure as possible form, typically better than 98.4%.

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2. The dissolving process is helped by shaking the solution for 1 hr. and storing at 37 °C for 12 hr.

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3. A separation of undissolved material is then reached by centrifuging at 2,500 rpm for 30 min.

Polymerization is lightly inhibited by utilizing trace amounts of an inhibitor (2

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drops) and the methylether of hydroquinone (MEHQ) is utilized for this purpose.

5. The Palmaz-Schatz stent and a Wiktor stent were used in this particular example. Other stents have been used in other tests.

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6. The stents were thoroughly cleaned using laboratory detergents, and washed in warm water.

7. The stents were left to air dry in a sterile environment (sterile lamina flow hood).

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8. The stents were then wetted with the solution by dipping them in the solution to the point where their entire surface was submerged in the liquid.

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 Using a specialty designed lever, the stents were lifted out of the solution at a rate of 1 mm/sec. This facilitated the uniformity of the coat.

The stents were left to air dry in a sterile environment (sterile lamina flow

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11. Steps 8-10 were repeated 4 times in order to get the appropriate coating thickness.

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12. The stents were moved to a UV light chamber and radiated for an additional 10 min. The stents were then placed in the chamber in a way that all sides of the stent were no more than 3 cm away from each lamp.

- 13. In order to remove any remaining HEMA monomer and/or traces of the inhibitor after the polymerization step, the stent was boiled in water for about 2 to 3 minutes after cooling down.
- 14. After boiling, the stents were dried at a slightly higher temperature.
- 15. The stents were then placed on an angioplasty balloon and were inflated to 85% of their range.
- 16. The stents were weighed and examined under a scanning microscope to determine the uniformity of the coat and its attachment to the stent surface.
- 17. The stents' surface appeared to be completely covered and to a sufficient level of uniformity. Coating adhesion remained intact even under severe stress.

Example 2

- 1. A stock solution was prepared by dissolving 120 mg poly-hydroxyethyl methacrylate (PHEMA) IN 1 ML 95% ethanol. It is preferable to use the PHEMA in an as pure as possible form, typically better than 98.4%.
- 2. The dissolving process was helped by heating the solution to 75 °C and shaking the solution for 1 hr.
- A separation of undissolved material was reached by centrifuging at 3.g.
 2500 rpm for 30 min.
- 4. The Palmaz-Schatz stent and a Wiktor stent were used in this particular example. Other stents have been used in other tests.
- The stents were thoroughly cleaned using laboratory detergents and washed in warm water.
- The stents were left to air dry in a sterile environment (sterile lamina flow hood).
- 7. The stents were then wetted with the solution by dipping them in the solution to the point where their entire surface was submerged in the liquid.

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Using a specially designed lever, the stents were lifted out of the solution at 8. a rate of 1 mm/sec. This facilitated the uniformity of the coat.

The stents were left to air dry in a sterile environment (sterile lamina flow 9. hood) for 15 min. Steps 7-9 were repeated 4 times in order to obtain the appropriate coating 10.

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- thickness. The stent was boiled in water for about 2 to 3 minutes.
- 12. After boiling, the stents were then air-dried at a slightly higher temperature.
- The stents were then placed on an angioplasty balloon and were inflated to 13. 85% of their range.

intended to be embraced therein.

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The stents were weighed and examined under a scanning microscope to 14. determine the uniformity of the coat and its attachment to the stent surface.

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The stents' surface appeared to be completely covered and to a sufficient level of uniformity. Coating adhesion remained intact even under severe stress.

It will be evident to those skilled in the art that the invention is not limited to the

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details of the foregoing illustrative examples and that the present invention may be embodied in other specific forms without departing from the essential attributes thereof, and it is therefore desired that the present embodiments and examples be considered in all respects as illustrative and not restrictive, reference being made to the appended claims, rather than to the foregoing description, and all changes which

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come within the meaning and range of equivalency of the claims are therefore

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Claims

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A hemo-compatible, restenosis-inhibiting metallic stent according to claim 1,

WHAT IS CLAIMED IS:

mixtures thereof.

2.

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 A hemo-compatible, restenosis-inhibiting metallic stent, comprising a coating of a poly-hydroxy methacrylate derivative.

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comprising a coating of a poly-hydroxy methacrylate derivative selected from the group consisting of poly-hydroxyethylmethacrylate (PHEMA), poly (hydroxyethoxyethyl methacrylate) (PHEEMA), poly (hydroxydiethoxyethyl methacrylate) (PHDEEMA), poly (methoxyethyl methacrylate) (PMEMA), poly (methoxyethoxyethyl methacrylate) PMEEMA, poly (methoxydiethoxyethyl methacrylate) (PMDEEMA), poly (ethylene glycol dimethacrylate) (PEGDMA), and

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3. A process for producing hemo-compatible, restenosis inhibiting metallic stents comprising the steps of:

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(a) coating a metallic stent with a liquid which contains a hydroxymethacrylate derivative selected from the group consisting of 2-hydroxyethyl-methacrylate; hydroxyethoxyethyl methacrylate, hydroxydiethoxyethyl methacrylate, methoxyethyl methacrylate, ethylene

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glycol dimethacrylate and mixtures thereof;

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polyhydroxymethacrylate derivative selected from the group consisting of poly-hydroxyethylmethacrylate (PHEMA), poly (hydroxyethoxyethyl methacrylate)

(b) polymerization of said 2-hydroxy-methacrylate derivative into a

(PHEEMA), poly (hydroxydiethoxyethyl methacrylate) (PHDEEMA), poly (methoxyethyl methacrylate) (PMEMA), poly (methoxyethyl methacrylate) PMEEMA, poly (methoxydiethoxyethyl methacrylate) (PMDEEMA), poly (ethylene glycol dimethacrylate) (PEGDMA), and mixtures thereof; and

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- (c) cleaning the stent after polymerization to extract any remaining residues.
- 4. The process of claim 3 wherein the stent is cleaned in warm water.

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10	5. linking a	The process of claim 3 comprising the additional step of adding a cross agent.
	6. amount	The process of claim 5, wherein said cross linking agent is present in an of about 0.1% to 6% weight relative to the weight of the
15	2-hydro	xyethyl-methacrylate monomer.
	7.	The process of claim 3 wherein the stent is first treated with a primer.
	8.	The process of claim 3 wherein the stent is made from a metal in
20 .	combina	ation with a polymer.
	9.	The process of claim 3 wherein the stent is made from stainless steel.
	10.	The process of claim 3 wherein the stent is made from a Ti-based alloy.
25	11. alloy.	The process of claim 3 wherein the stent is made from a shape memory
30	12 _. atmosp	The process of claim 3 wherein the polymerization is carried out at heric pressure.
	13. dielectr	The process of claim 3 wherein the polymerization is carried out by ic heating.
35	14.	The process of claim 3 wherein the polymerization is carried out by on heating.
40	15. one of p	The process of claim 3 wherein the polymerization is initiated by at least photopolymerization, ionic-polymerization, and chemical-polymerization.
	16. elevate	The process of claim 3 wherein the polymerization is carried out at d pressures.
1 5	17. tempera	The process of claim 3 wherein the polymerization is carried out at at atures in the range of 150°C to 230°C.
	1Ω	The process of claim 5, wherein said cross linking agent is methacrylic

diester of ethyleneglycol.

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	19.	The process of claim 18, wherein said methacrylic diester of ethyleneglycol
10	is selec	ted from the group consisting of:
* .	(a)	tetraethyleneglycol dimetacrylate,
	(b)	triethyleneglycol dimethacrylate,
15	(c)	diethyleneglycol dimethacrylate,
	(d)	monoethyleneglycol dimethacrylate, and
	(e)	mixtures thereof.
	20.	The process of claim 3, wherein said poly-hydroxyethylmethacrylate
20	compris	ses a copolymer of monomeric 2-hydroxyethyl-methacrylate.
	21.	The process of claim 20, wherein said coating contains a cross linking
·	agent.	
25	22.	The process of claim 3 wherein NaOH is added before said polymerization
·	step.	
	23.	The process of claim 22, wherein said at least 30% NaOH is used.
30	24.	The process of claim 22, wherein said polymerization is effected at a
	tempera	ature of at least 90°C.
	25.	The process of claim 3, comprising diluting said
35	poly-hy	droxyethylmethacrylate containing liquid in order to obtain different coating
	thickne	sses.
	26.	A process for producing hemo-compatible bioactive restenosis inhibiting
40	metallio	stents, comprising the steps of:
	a)	coating a metallic stent with a liquid which contains
	poly-hy	droxyethylmethacrylate in liquid form;
45	b)	cleaning the stent to extract any remaining toxic residues; and

c)

drying the same.

INTERNATIONAL SEARCH REPORT

PCT/IL 99/00376

A. CLASS	SIFICATION OF SUBJECT MATTER A61L31/10		
According	to international Patent Classification (IPC) or to both national da	ssification and IPC	
	SEARCHED		
Minimum of IPC 7	ocumentation searched (class#ication system followed by class A61L	ulication symbole;	
Documenta	ation searched other than maximum documentation to the extent	that such documents are included in the fields s	earched
Electronic	data base consulted during the international search (name of da	ita base and, where practical, search terms used	ŋ
	· ·		
C. DOCUM	ENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the	he relevant passages	Relevant to claim No.
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	page 15, line 19 -page 16, lin	e 14	
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* Special ca	stegories of cited documents :	"I later document published after the inte or priority date and not in conflict with	mational liling date
"A" docum	ent defining the general state of the lart which is not Sered to be of particular relevance	cited to understand the principle or th	the application but sory underlying the
"E" earlier	document but published on or after the international	Invention "X" document of particular relevance; the o	laimed invention
filing o	ent which may throw doubts on priority claim(s) or	cannot be considered novel or cannot involve an inventive step when the do	be considered to current is taken alone
citatio	is cited to establish the publication date of another in or other special reason (as apecified)	"Y" document of particular relevance; the c cannot be considered to involve an in	ventive step when the
	ent referring to an oral disclosure, use, exhibition or means	document is combined with one or mo ments, such combination being obvio	re other such docu-
"P" docum	ent published prior to the international filing date but han the phority date claimed	in the art. "&" document momber of the same patent	
	actual completion of the international search	Date of mailing of the international se	
2	6 October 1999	04/11/1999	•
Name and	making address of the ISA	Authorized officer	
	European Patent Office, P.B. 5818 Patentinon 2		
	Tel. (+31-70) 340-2040, Tx. 31 651 epo ni,	Heck, G	•
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